# Clinical studies with high flow nasal cannula oxygen delivery in 2015

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We identified 21 clinical studies, including six in Respiratory Care, using high flow nasal cannula oxygenation (HFNC) published between January 1, 2015, and January 31, 2016. Seven clinical studies were randomized controlled trials with patients in either intensive care units or emergency departments (Table 1).[1-7] Frat and coworkers reported a multicentered randomized controlled trial involving 310 patients with hypoxemic acute respiratory failure and a ratio of $PaO_2/FiO_2$ of 300 or less.[1] These patients were randomized to either HFNC with a flow rate of 50 L per minute and a $FiO_2$ of 1.0, or nonrebreathing masks with a rate of 10 L per minute or more, or noninvasive ventilation (NIV) with adjustment of the $FiO_2$ to maintain an oxygenation goal of 92% saturation or more. There were no differences in the time between the intervention to intubation and in the intubation rates in these three groups (primary outcome), but patients with a $PaO_2/FiO_2$ less than 200 had a decreased rate of intubation (post hoc analysis). The crude ICU mortality was lower in the HFNC group. The 90 day mortality rates were lower in patients in the HFNC group who did not require intubation. However, there were no differences in mortality in patients who required intubation. This study reported that ventilator-free days were higher in the HFNC group (24±8) compared to the nonrebreather study arm (22±10) and the NIV study arm (19±12). The authors concluded that the lower mortality rate noted with HFNC might have resulted from the reduced intubation rate in this group, especially in those with more severe respiratory failure and a $PaO_2/FiO_2$ ratio of less than 200. It was observed that patients who were treated with HFNC had more comfort, less dyspnea, and lower respiratory rates, and this was attributed to the possible effects of heat, humidification, and the level of PEEP created by the high flow rate of the inspired gas.

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Lemiale et al reported that HFNC oxygenation did not reduce the need for mechanical ventilation or improve patient comfort when compared to Venturi masks in immunocompromised patients with acute hypoxemic respiratory failure.[2] A noninferiority study conducted by Stephan and his colleagues between 2011 and 2014 compared HFNC and BiPAP using full facemasks in post cardiothoracic surgery patients who had acute respiratory failure, including failed spontaneous breathing trials and failed extubation following the surgery, or were at risk for acute respiratory failure.[4] This study included 830 patients randomized to either HFNC with an initial flow rate at 50 L per minute and $FiO_2$ fraction of 0.5 or BiPAP started at pressure support of 8 cm $H_2O$ to achieve a tidal volume of 8 ml/kg and respiratory rate of less than 25 breaths per minute for at least four hours per day with adjustments to keep $SaO_2$ at 92-98%. The rate of intubation was 21.0% (HFNC) and 21.9% (BiPAP). They found that HFNC support was not inferior to the use of BiPAP in these patients and concluded that the results support the use of HFNC in similar post-operative patients. Oxygenation was better with BiPAP (higher $PaO_2/FiO_2$ values) and that was thought due to higher positive end expiratory pressure. HFNC was associated with lower $PaCO_2$ possibly due to higher inspiratory flows and tidal volumes. The study reported no difference in the degree of discomfort or dyspnea

| **Table 1. Randomized trials** | | | | | | | |
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| **Author** | **Study design** | **#** | **Type of pts** | **Location** | **Intervention** | **Comparison** | **Outcomes** |
| Frat[1] | Multicenter, open-label, **RCT** | 310 | Hypoxemic ARF | ICU | HFNC started at 50 L/min $FiO_2$ 1.0 then adjusted to keep $O_2$ Sat ≥ 92. | Nonrebreather mask or NIV to keep $O_2$ Sat ≥ 92%. | No difference in intubation rates. Lower 90 day mortality in HFNC. |
| Lemiale[2] | Multi-center, parallel-group, **RCT** | 100 | Immunocompromised patients with hypoxemic ARF | ICU | HFNC with initial flow was 40–50 L/min with an $FiO_2$ of 100 %, then adjusted to maintain $SpO_2$ ≥95 %. | Venturi mask group with $FiO_2$ at 60 % at 15L/min initially, adjusted to maintain $SpO_2$ ≥ 95 %. | HFNC did not reduce the need for mechanical ventilatory assistance or improve patient comfort compared to oxygen delivered by a Venturi mask. |
| Vourc'h[3] | Multi-center, open-labelled, **RCT** | 124 | Hypoxemic ARF requiring intubation, random allocation to HFNC or HFFM. | ICU | HFNC preoxygenation for 4 min with HFNC set at 60 l/min flow, $FiO_2$ 100% | In the control group (HFFM), preoxygenation was performed for 4 min with high $FiO_2$ facial mask (15 l/min oxygen flow) | Compared to HFFM, HFNC preoxygenation did not reduce the lowest level of saturation. |
| Stéphan[4] | Multicenter, noninferiority trial, **RCT** | 830 | Post-cardiothoracic surgery ARF or at risk for ARF. | ICU | HFNC at 50 L/min, $FIO_2$ 50%, n = 414 | BiPAP with a full-face mask for at least 4 hours per day (IPAP 8 $cmH_2O$, EPAP 4 $cmH_2O$) $FIO_2$ 50%), n = 416 | High-flow nasal oxygen therapy was not inferior to BiPAP. |
| Rittayamai [5] | **RCT** | 40 | Acute dyspnea or hypoxemia | ED | HFNC at 35 L/min, FIO2 adjusted to achieve a $SpO_2$ of ≥94% within the first 5 min and was continued for 60 min. | $O_2$ was supplied via a nasal cannula or non-rebreathing mask at a flow of 3–10 L/min to maintain an $SpO_2$ of ≥ 94% for 60 min. | HFNC significantly improved dyspnea and comfort compared with conventional oxygen therapy. |
| Bell[6] | **RCT** | 100 | Acute dyspnea | ED | HFNC | Standard $O_2$ | Reduced RR (67% vs 39%), Lower % requiring an escalation in therapy (4.2% vs 19%) |
| Jones[7] | Pragmatic, open label **RCT** | 303 | Hypoxemic AFR | ED | HFNC at 40 L/min, $FiO_2$ 28%. | Standard $O_2$ with Venturi device, or nasal prongs using wall oxygen titrated with a flow meter(1–15 L/min). | Lower rate of intubation with HFNC (p=0.16). No difference in mortality or hospital LOS |

ARF- acute respiratory failure, BiPAP- bilevel positive airway pressure, ED- emergency department, EPAP- expiratory airway pressure, HFNC- high flow nasal cannula oxygen, HFFM- high flow face mask, ICU- intensive care unit, IPAP- inspiratory positive airway pressure, LOS- length of stay, NIV- noninvasive ventilation, NA- not applicable, RCT-randomized controlled trial

| **Table 2 Retrospective studies** | | | | | | | |
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| **Author** | **Study design** | **#** | **Type of pts** | **Location** | **Intervention** | **Comparison** | **Outcomes** |
| Hyun Cho[8] | Retrospective | 75 | Acute hypoxemic respiratory failure | ICU | Blended gases at 30-40 L/min and $FiO_2$ of 40-100% using a HFNC device. The primary therapeutic goal was $SpO_2$ >92% or $PO_2$ > 65 mmHg. | N/A | 37.3% intubated, 25.3% mortality. HFNC improved $PaO_2$, RR, HR, throughout the first 24 hours. |
| Nagata[9] | Retrospective | 172 | Hypoxemic respiratory failure | ICU Intermediate care unit Hospital | HFNC | Conventional oxygen therapy | No change in mortality, hospital LOS, mechanical ventilation ($p<0.01$). |
| Sotello[10] | Retrospective | 106 | Respiratory failure | ICU Intermediate care unit Hospital | HFNC use, patients were subdivided into 2 subgroups: a step-up group ( patients switched from standard $O_2$ to HFNC), and a step-down group (patients transitioned from NIV and/or mechanical ventilation to HFNC) | NA | $PO_2$ and $O_2$ saturations improved when patients were switched to HFNC in the step-up group. No significant difference between $PO_2$ and $O_2$ saturations in Step- down group. |
| Messika[11] | Prospective data, retrospective review | 560 | ARDS | ICU | HFNC | | HFNC was used in 45 subjects with ARDS, only 40% required secondary intubation |
| Yoo[12] | Retrospective cohort | 73 | Post extubation respiratory failure | ICU | HFNC | NIV ( historical cohort) | No difference in reintubation rate (79.4% vs 66.7%), ICU stay shorter in HFNC group |
| Roca[13] | Prospective data, retrospective review | 37 | Lung transplantation with ARF | ICU | HFNC | Conventional $O_2$ | Relative risk for mechanical ventilation higher in $O_2$ group (1.5), NNT=3 |
| Gaunt[14] | Retrospective | 145 | Hypoxemic ARF | ICU | Initial settings at 50 L/min and 50% $FIO_2$ | Mechanical ventilation prior to HFNC | Intubation rate 20%, Reintubation 20% vs 20%, Mortality 14.5% vs. 11.4%. Early HFNC may be beneficial |

ARDS- acute respiratory distress syndrome, ARF- acute respiratory failure, ED- emergency department, HFNC- high flow nasal cannula oxygen, HR- heart rate, ICU- intensive care unit, NA- not applicable, NIV- noninvasive ventilation, RR-respiratory rate between the two groups. Vourc'h compared preoxygenation with either HFNC or high flow facemasks in hypoxemic patients requiring intubation.[3] There was no difference in oxygenation status prior to intubation in these two groups. Several studies have evaluated the use of HFNC in emergency departments (ED).[5-7] This method appears to significantly improve oxygenation and dyspnea when compared to conventional oxygen therapy; it reduces respiratory rates and possibly the need for an escalation in therapeutic support. It does not appear to have a significant effect on intubation rates, mortality, or hospital length of stay in ED patients. These randomized trials suggest that high flow nasal cannulas provide a good method for oxygen delivery to patients with acute respiratory failure, acute respiratory distress in the ED, and in postoperative patients. Outcomes were better in the Frat study in patients with lower $PaO_2/FiO_2$ ratios.

Seven articles provided retrospective reviews of HFNC use in hospitalized patients (Table 2).[8-14] Most of these patients were in intensive care units. Two articles compared HFNC use with conventional oxygen use; one compared it with noninvasive ventilation based on a historical cohort.[9,12,13] In general, oxygen delivery with HFNC increased the $PaO_2$, reduced the respiratory rate, and reduced heart rates. Most of the studies found no important difference in outcomes, but one study with 37 lung transplant patients who required ICU readmission for acute respiratory failure found that HFNC oxygen delivery reduced the risk for mechanical ventilation (OR 0.43 [95% CI: 0.002-0.88], P=0.04) when compared to conventional oxygenation.[13] Additionally, patients treated with HFNC who did not need mechanical ventilation had a higher survival. The relative risk for requiring mechanical ventilation in the conventional oxygen therapy group was 1.5 (1.02-2.21). The absolute risk reduction for mechanical ventilation was 29.8% in the HFNC group, and the number needed to treat to prevent one intubation was three.Patients who failed HFNC treatment had more infiltrates on chest x-ray and had more frequent ARDS and shock during their ICU stays. Gaunt et al suggested that early use of HFNC may be beneficial in hypoxemic patients with acute respiratory failure to provide better support during the early phase of treatment.[14] Retrospective studies have important limitations, but the results in lung transplantation patients are potentially important and need confirmation.

Four studies evaluated the physiological effects of HFNC use, and three studies identified factors associated with failure during HFNC use (Table 3).[15-21] Jeong studied 973 patients with acute respiratory failure in an emergency department.[15] These investigators demonstrated that HFNC use could decrease the $PaCO_2$ in patients who presented to the emergency department with $PaCO_2$ greater than 45 mmHg. Vargas et al did relatively complex studies in 12 patients with acute respiratory failure and measured esophageal pressures, breathing patterns, gas exchange, and symptoms.[18] High flow nasal cannula use was compared to nonrebreathing masks and to CPAP. High flow nasal cannula use reduced the inspiratory effort and improved oxygenation when compared to conventional $O_2$ therapy. However, patients on the CPAP had bigger increases in $PaO_2/FiO_2$ ratios. Frat demonstrated that HFNC use was better tolerated than noninvasive ventilation in patients with acute respiratory failure in the medical intensive care units.[17] However, $PaO_2$ increased more with noninvasive ventilation. High flow nasal cannula use has been used in stable COPD patients and compared to noninvasive ventilation.[16] Both strategies reduce the resting $PaCO_2$.

Patients on $O_2$ delivered by HFNC need frequent and careful evaluation for progression of their respiratory failure and respiratory muscle fatigue. Koga used a multivariable model to identify factors associated with HFNC failure.[19] Failure was defined by the need for intubation or to switch to NIV after HFNC use. This model demonstrated that larger pleural effusions and higher SOFA scores were associated with HFNC failure. In a previous study, the lack of initial response to HFNC, more severe disease, and additional organ dysfunction are associated with increased risk of HFNC failure.[11] Lee reported that patients with hematologic malignancies and acute respiratory failure would more likely require intubation if they had bacte-

| Table 3 Physiologic studies and factors associated with HFNC failure | | | | | | | |
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| **Author** | **Study design** | **#** | **Type of pts** | **Location** | **Intervention** | **Comparison** | **Outcome** |
| Physiological studies | | | | | | | |
| Jeong[15] | Retrospective | 173 | ARF | ED | HFNC | NA | $PCO_2$ decreased in patients with $PCO_2$ > 45 |
| Bräunlich[16] | Prospective, non-randomized crossover | 11 | COPD | Outpatient | HFNC 20 L/min | NIV | NFNC led to significant decreases in resting $PCO_2$, Between the devices we found no differences in $pCO_2$ levels. |
| Frat[17] | Prospective, crossover | 28 | ARF | ICU | HFNC | NIV after HFNC | $PO_2$ increased more with NIV, HFNC tolerated better |
| Vargas[18] | Prospective | 12 | ARF | ICU | HFNC at 60 L/min, esophageal pressure, breathing pattern, gas exchange, comfort, dyspnea were measured. | Non-re-breathing mask to keep $O_2$ Sat >90%, CPAP at 5 cm $H_2O$ | Compared to conventional $O_2$ therapy, HFNC improved inspiratory effort and oxygenation, CPAP increased $PaO_2/FIO_2$ more |
| Factors associated with HFNC failure | | | | | | | |
| Koga[19] | Retrospective | 73 | ARF | ICU | HFNC | NA | The extent of pleural effusion and the SOFA score were associated with HFNC failure |
| Lee[20] | Retrospective | 45 | ARF[1] | ICU | HFNC | NA | Patients with bacterial pneumonia more likely to fail HFNC |
| Kang[21] | Retrospective | 175 | ARF | ICU | HFNC | NA | Intubation >48 hr after HFNC use and failure increased mortality |

[1]with hematologic malignancy, ARF- acute respiratory failure, ED- emergency department, HFNC- high flow nasal cannula oxygen, ICU- intensive care unit, NA- not applicable, NIV- noninvasive ventilation, SOFA- sequential organ failure assessment

rial pneumonia.[20] Kang reported that intubation more than 48 hours after HFNC use and failure was associated with increased mortality.[21] Roca et al concluded that ARDS, renal failure, and addition of vasopressors are predictors of HFNC failure and associated with an increased risk of intubation and mortality. [13]

In summary, HFNC devices can provide humidified oxygen at high flow rates with high $FiO_2$s. This method of oxygen delivery appears to be more comfortable than using noninvasive ventilation, and it does improve oxygenation, reduce respiratory rates, and reduce the sense of dyspnea. This modality has been studied most in patients with acute hypoxemic respiratory failure. The study reported by Frat et al provides good evidence that patients with moderate to severe respiratory failure ($PaO_2/FiO_2$ < 200) may benefit the most.[1] Patients on HFNC need careful monitoring and early recognition of predictors of treatment failure to avoid prolonged use with ultimate and delayed intubation and worse outcomes. The more complex the patient's underlying medical problems are the more likely HFNC therapy to fail.[19-21]

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## References

1. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015 Jun 4; 372(23):2185-96.
2. Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. Crit Care 2015 Nov 2; 19:380.
3. Vourc'h M, Asfar P, Volteau C, et al. High-flow nasal cannula oxygen during endotracheal intubation in hypoxemic patients: a randomized controlled clinical trial. Intensive Care Med 2015 Sep; 41(9):1538-48.
4. Stéphan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. JAMA 2015 Jun 16; 313(23):2331-9.
5. Rittayamai N, Tscheikuna J, Praphruetkit N, et al. Use of high-flow nasal cannula for acute dyspnea and hypoxemia in the emergency department. Respir Care 2015 Oct; 60(10):1377-82.
6. Bell N, Hutchinson CL, Green TC, et al. Randomized control trial of humidified high flow nasal cannulae versus standard oxygen in the emergency department. Emerg Med Australas 2015 Sep 29.
7. Jones PG, Kamona S, Doran O, et al. Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: The HOT-ER Study. Respir Care 2015 Nov 17.
8. Hyun Cho W, Ju Yeo H, Hoon Yoon S, et al. High-flow nasal cannula therapy for acute hypoxemic respiratory failure in adults: a retrospective analysis. Intern Med 2015; 54(18):2307-13.
9. Nagata K, Morimoto T, Fujimoto D, et al. Efficacy of high-flow nasal cannula therapy in acute hypoxemic respiratory failure: decreased use of mechanical ventilation. Respir Care 2015 Oct; 60(10):1390-6.
10. Sotello D, Orellana-Barrios M, Rivas AM, et al. High flow nasal cannulas for oxygenation: an audit of its use in a tertiary care hospital. Am J Med Sci 2015 Oct; 350(4):308-12.
11. Messika J, Ben Ahmed K, Gaudry S, et al. Use of high-flow nasal cannula oxygen therapy in subjects with ARDS: A 1-year observational study. Respir Care 2015 Feb; 60(2):162-9.
12. Yoo JW, Synn A, Huh JW, et al. Clinical efficacy of high-flow nasal cannula compared to noninvasive ventilation in patients with post-extubation respiratory failure. Korean J Intern Med 2016 Jan; 31(1):82-8.
13. Roca O, de Acilu MG, Caralt B, et al. Humidified high flow nasal cannula supportive therapy improves outcomes in lung transplant recipients readmitted to the intensive care unit because of acute respiratory failure. Transplantation 2015 May; 99(5):1092-8.
14. Gaunt KA, Spilman SK, Halub ME, et al. High-flow nasal cannula in a mixed adult ICU. Respir Care 2015 Oct; 60(10):1383-9.
15. Jeong JH, Kim DH, Kim SC, et al. Changes in arterial blood gases after use of high-flow nasal cannula therapy in the ED. Am J Emerg Med 2015 Oct; 33(10):1344-9.
16. Bräunlich J, Seyfarth HJ, Wirtz H. Nasal High-flow versus non-invasive ventilation in stable hypercapnic COPD: a preliminary report. Multidiscip Respir Med 2015 Sep 3; 10(1):27.
17. Frat JP, Brugiere B, Ragot S, et al. Sequential application of oxygen therapy via high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. Respir Care 2015 Feb; 60(2):170-8.
18. Vargas F, Saint-Leger M, Boyer A, et al. Physiologic effects of high-flow nasal cannula oxygen in critical care subjects. Respir Care 2015 Oct; 60(10):1369-76.
19. Koga Y, Kaneda K, Mizuguchi I, et al. Extent of pleural effusion on chest radiograph is associated with failure of high-flow nasal cannula oxygen therapy. J Crit Care 2015 Dec 11.
20. Lee HY, Rhee CK, Lee JW. Feasibility of high-flow nasal cannula oxygen therapy for acute respiratory failure in patients with hematologic malignancies: A retrospective single-center study. J Crit Care 2015 Aug; 30(4):773-7.
21. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015 Apr; 41(4):623-32.